REMARKS

Claims 1 through 30 continue to be in the case.

New claim 31 is being presented. New claim 31 is based on the language of claim 2.

Applicants want to present some additional considerations in connection with the present application.

Applicants note relating to the influence of shearing forces the following:

The shearing forces have a decisive influence on the growth, especially in the sense of a cell division of the endothel cells. The important and valuable properties for the product furnishing influence onto the growth rests in the functional change of the cells, amongst others the elongation and the orientation of the cells along the attacking shearing forces and the formation of an improved adherence, that is a adherence of the cells on the prothesis surface. Corresponding suggestions to the general

influence of the shearing forces of the endothel cells can be gathered from the literature as follows:

[1] Cheng S., Song Li, J. Shyy: Effects of mechanical forces on signal construction and gene expression in endothelial cells. Hypertension 1998, 31: 162 -- 69

[2]Chappel D., S. Varner et al.: Oscillatory shear stress simulates adhesion molecule expression in cultured human endothelium. Circ.Res. 1998, 82: 532 -- 539

[3] Schnittler H., b. Pueschel, D. Drenckhahn: role ofcadherins and plakoglobin in inter-endothelial adhesion under arresting conditions and shear stress. Am. J. Physiol. 1997, 273 (heart circ. Physiol): H 2396 --H 2405,

There is further the question if the endothel cells according to the present invention have a particular cell density or a particular pattern relative to the teaching of the patent application WO 93/01843?

The answer to the question is that. there is a particular pattern in the cell growth and in the cell density in the case of the present patent application. The initial cell density amounts to 30 to 50 percent in homogeneous distribution and the final cell density amounts in fact one hundred percent and in fact prior to and after the implantation, that means also a surface covering in contrast to the above application reference, WO 93/01843, p. 8, line 13. Since the cells have been adapted already in vitro, that is in the perfusion circulation to the flow conditions prevailing in vivo, that is in the blood vessel, after transplantation of the prothesis in to the blood circulation no cells any longer dissolve off. The cells exhibit a clearly stronger adherence based on the sub confluent initial cell seeding and the growth to confluent under shear forces rising up to physiological values, which furnishes unique properties to the product based on the describe method, namely the stable adhesion of the cells on the surface of the prothesis.

A definition of the word prothesis can be as follows:

A prothesis is an artificially prepared organ, frequently as a substitute for a lacking or a defect organ, but also as an additional organ as required according to medical indication, wherein the organ is limited here by the addition of the word "cardiovascular" to the heart and vessel region. The term prothesis comprises therefore by way of example all blood conductors and vessels such as the immediate replacement of vessels (venes, arteries) and blood conductors with medical indication such as AV-shunts but also more complex organs such as heart flaps.

Reconsideration of all outstanding rejections is respectfully requested.

Respectfully submitted,

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MARKED-UP VERSION OF THE AMENDED CLAIMS

(Version with marking to show changes made)

1. (previously presented) Cardiovascular prostheses with an endothelial cell surface produced in that after an initial sub-confluent seeding of a surface on the blood contact side, the formation of a confluent monolayer ensues by the cells growing under a permanent influence of defined pulsatile shear forces increasing up to physiological values, by means of streaming the prosthesis surface on the blood contact side along a main axis of the prosthesis in an inner perfusion circuit and by moistening an outer prosthesis wall in an outer perfusion circuit, or in a permeable medium reservoir.

2. (original) Cardiovascular prostheses according to claim 1, characterized in that the increasing shear forces are generated by means of a program-controlled pumping device (7).

3. (previously presented) Cardiovascular prostheses according to claim 1, characterized in that the mathematical value of the increasing shear forces can be selected variably and time-independently.

4. (previously presented) Cardiovascular prostheses according to claim 1, characterized in that the mathematical value and the final value of the shear forces can be selected freely and time-variably by means of a program control according to the physiological conditions of the implantation location.

5. (previously presented) Cardiovascular prostheses according to claim 1, characterized in that the mathematical value of the occurring shear forces can be adjusted by varying pumping capacity, as well as by varying the size of the cross-section of pumping tubes used or of any other connecting elements outside of the chamber, as well as by the geometrical form and configuration of the very chamber.

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6. (previously presented) Cardiovascular prostheses according to claim 1, produced by means of a perfusion circuit consisting of an inner perfusion circuit (5) for streaming the prosthesis surface on the blood contact side along the main axis of the prosthesis inside of the chamber (2), said prosthesis (1) being fixed in the inner space thereof by means of

adapters (3, 3'), and hence constituting as such the inner perfusion circuit (5), and an outer perfusion circuit (5') for outwardly streaming the prosthesis (1) within the same chamber (2) which comprises, towards the outside, connections to a pumping device (7) for both circuits (5, 5'), as well as to the medium reservoirs (6, 6') which also have the function of pressure equation reservoirs.

7. (previously presented) Cardiovascular prostheses according to claim 1, produced by means of a perfusion circuit consisting of an inner perfusion circuit (5) for streaming the prosthesis surface on the blood contact side along the main axis of the prosthesis inside of the chamber (2), said prosthesis (1) being fixed in the inner space thereof by means of an adapter (3), and hence constituting as such the inner perfusion circuit (5), and an outer perfusion circuit (5') uniting inside of the chamber (2) with the inner perfusion circuit (5) after having streamed the prosthesis (1) for outwardly streaming the prosthesis (1) within the same chamber (2) which comprises, towards the outside, connectors to a pumping device (7) for both circuits (5, 5'), as well as to the medium reservoirs (6, 6') which also have the function of pressure equation reservoir.

8. (previously presented) Cardiovascular prostheses according to claim 6, characterized in that the outer perfusion circuit (5') can be operated by a method selected from the group consisting of co-current transporting to the inner perfusion circuit (5), counter-current transporting to the inner perfusion circuit (5), and static transporting to the inner perfusion circuit (5).

9. (previously presented) Cardiovascular prostheses according to claim 6, characterized in that the perfusion circuits lead from one medium reservoir (6) into another medium reservoir (6'), in which the medium collected has already streamed through the prosthesis.

10. (previously presented) Cardiovascular prostheses according to claim 6, characterized in that the inner and the outer perfusion circuits have different medium reservoirs or one and the same medium reservoir (6, 6').

11. (previously presented) Cardiovascular prostheses according to claim 6, characterized in that the prosthesis is present in the very medium

reservoir, and that the inner and the outer perfusion circuits are thereby connected with each another.

12. (previously presented) Cardiovascular prostheses according to claim 6, characterized in that the medium reservoirs are comprised of expandable blood bags of the materials PVC or EVAM.

13. (previously presented) Cardiovascular prostheses according to claim 6, characterized in that the realization of the adapters (3, 3') for fixing the prosthesis (1) is realized by an olive .

14. (previously presented) Cardiovascular prostheses according to claim 6, characterized in that the length of the prosthesis to be clamped can be varied by constructionally providing at least one closing part with the adapter (3 or 3') of chamber (2).

15. (previously presented) Cardiovascular prostheses according to claim 6, characterized in that the chamber (2) is manufactured from a transparent material.

16. (previously presented) Cardiovascular prostheses according to claim 1, characterized in that the prosthesis is used as a member selected from the group consisting of a vascular prosthesis, a heart valve prosthesis and a stent.

17. (previously presented) Method for covering cardiovascular prostheses with endothelial cells according to claim 1, characterized in that after an initial sub-confluent seeding of the prosthesis surface on the blood contact side, the formation of a confluent monolayer ensues by the cells growing under permanent influence of defined pulsatile shear forces increasing up to physiological values by means of streaming the prosthesis surface on the blood contact side along the main axis of the prosthesis in an inner perfusion circuit, and a moistening of the outer prosthesis wall in an outer perfusion circuit or in a permeable medium reservoir.

18. (original) The method according to claim 17, characterized in that

a) the increasing shear forces are generated by means of a program-controlled pumping device (7),

b) the mathematical value of the increasing shear forces can be selected variably and time-independently,

c) the mathematical value and the final value of the shear forces can be selected freely and time-variably by a program control according to the physiological conditions of the implantation location, and

d) the mathematical value of the arising shear forces can be adjusted by varying the pumping capacity, as well as by varying the size of the cross-section of the pumping tubes used or of any other connecting elements outside of the chamber, as well as by the geometrical form and configuration of the very chamber.

19. (previously presented) The method according to claim 17, characterized in that in an inner perfusion circuit (5) for streaming through the inner prosthesis space along the main axis of the prosthesis inside of the chamber (2), the prosthesis (1) is fixed by means of adapters (3, 3'), and hence as such constitutes the inner perfusion circuit (5), and that an outer perfusion circuit (5') exists for outwardly streaming the prosthesis (1) in the same chamber (2) which, towards the outside, comprises for the two circuits (5, 5') connectors to a pumping device (7) and medium reservoirs (6, 6') which also have the function of pressure equation reservoirs.

20. (previously presented) The method according to claim 17, characterized in that

a) the outer perfusion circuit (5') can be operated in co-current or counter-current to the inner perfusion circuit (5), but also statically,

b) the two perfusion circuits (5, 5') do not work as a closed system but lead from one medium reservoir (6) into another medium reservoir (6'), in which the medium collected has already streamed through the prosthesis,

c) the inner and the outer perfusion circuits have a member selected of the group consisting of different medium reservoirs and one and the same medium reservoir (6, 6'), and

d) the two perfusion circuits (5, 5') unite inside the chamber (2) after having streamed the prosthesis (1), but leave the chamber (2) in separate perfusion circuits (5, 5').

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21. (previously presented) The method according to claim 17, characterized in that the prosthesis is present in the very medium reservoir and that the inner and the outer perfusion circuits are thereby connected with each another.

22. (previously presented) Cardiovascular prostheses according to claim 6, characterized in that the realization of the adapters (3, 3') for fixing the prosthesis (1) is realized by cones with clamping means.

23. (previously presented) Cardiovascular prostheses according to claim 6, characterized in that the realization of the adapters (3, 3') for fixing the prosthesis (1) is realized by an expansion member.

24. (previously presented) Cardiovascular prostheses comprising an endothelial cell surface produced wherein the formation of a confluent monolayer ensues by the cells growing under a permanent influence of defined pulsatile shear forces increasing up to physiological values after an initial sub-confluent seeding of a surface on the blood contact side, by means of streaming the prosthesis surface on the blood contact side along a main axis of the prosthesis in an inner perfusion circuit and by moistening an outer prosthesis wall in an outer perfusion circuit, or in a permeable medium reservoir.

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25. (previously presented) The cardiovascular prostheses according to claim 24 wherein the shear force is from about 0.01 to 5 dyn/cm2.

26. (previously presented) The cardiovascular prostheses according to claim 24 wherein a confluent endothelial layer having a high quality is present.

27. (previously presented) A method for covering cardiovascular prostheses with endothelial cells comprising the following steps:

initially sub-confluently seeding the prosthesis surface on the blood contact side;

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streaming the prosthesis surface on the blood contact side along the main axis of the prosthesis in an inner perfusion circuit, and a moistening of the outer prosthesis wall in an outer perfusion circuit or in a permeable medium reservoir;

growing cells growing under a permanent influence of defined pulsatile shear force increasing up to physiological values;

forming a confluent monolayer of the grown cells.

28. (previously presented) The method for covering cardiovascular prostheses according to claim 27 further comprising employing a shear force from about 0.01 to 5 dyn/cm2.

29. (previously presented) The method for covering cardiovascular prostheses according to claim 27 further comprising forming a confluent endothelial layer having a high quality.

30. (previously presented) The method for covering cardiovascular prostheses according to claim 27 further comprising

varying pumping capacity for adjusting the size of occurring shear forces.

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Cancel 31. (new) The method for covering cardiovascular prostheses according to claim 27 further comprising

generating increasing shear forces by means of a program-controlled pumping device (7).